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| 09/300,425 | 04/28/1999 | DARIO NERI | 113000.301 | 4446 |
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EXAMINER

PORTNER, VIRGINIA ALLEN

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1645

DATE MAILED: 09/04/2002

29

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/300,425

Applicant(s)

Neri et al

Examiner

Portner

Art Unit

1645



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on May 28, 2002
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 14-17 and 19-39 is/are pending in the application.
- 4a) Of the above, claim(s) 14-17, 19, and 25-27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 20-24, 28-37, and 39 is/are rejected.
- 7) ☒ Claim(s) 38 is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

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**DETAILED ACTION**

Claims 14-17, 19-27, 28-39 are pending.

Claims 20-24 and 28-39 are under consideration.

Claims 14-17, 19 and 25-27 stand withdrawn from consideration.

***Continued Prosecution Application***

1. The request filed on May 28, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/300,425 is acceptable and a CPA has been established. An action on the CPA follows.

***Allowable Subject Matter***

2. Claim 38 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Rejections Maintained***

3. Claims 20-24 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because claim 20 still recites the an abbreviation "ED-B" for reasons of record in paper number 15, paragraph 15, subparagraph c.

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4. Claims 20-23, new claims 33, 34 and 35( (see Neri et al, page 23, line 35, figure 1b, alignment, aa 94-96) are rejected under 35 U.S.C. 102(b) as being anticipated by **Neri et al** (WO97/45544, reference provided in Applicant's 1449) for reasons of record in paper number 15, paragraph 12.
5. Claims 20-24, and new claims 28-37 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neri et al (WO97/45544, reference provided in Applicant's 1449) in view of Theodore et al (US Pat. 6,015,897)for reasons of record in paper number 15, paragraph 16.

***Specification***

6. The title of the invention is still not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Reference to Fibronectin extra domain B would describe the invention more clearly.
7. The Brief Description of the Drawings and the figures shown do not evidence clear labels and description of the contents of the figures see 37 CFR 1.74, 37 CFR 1.81, 1.83-1.85, and MPEP § 608.02.
  - a. Figure 1A & 1B should be recited and briefly described.

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- b. Figure 2A & 2B should be recited and briefly described.
- c. Figure 3 A,B &C should be recited and briefly described.
- d. Figure 4 A,B &C should be recited and briefly described
- e. Figure 7, each frame (A-H) should be labeled and briefly described. Figure 7 shows several abbreviations. These abbreviations should be defined in the Brief Description of the Drawings. Clarification of the abbreviations is requested.
- f. Figure 9 A,B &C should be recited and briefly described.
- g. Figure 10 A,B, C & D should be recited and briefly described.
- h. Figure 11 A, B,C,D,E,F,G,H,I,J,K & L should be recited and briefly described.
- i. Figure 12 A, B,C,D,E,F,G,H,I,J,K & L should be recited and briefly described.

***Response to Arguments***

- 8. Applicant's arguments filed March 28, 2001 have been fully considered but they are not persuasive.
- 9. The rejection of claims 20-23 and new claims 33-35 rejected under 35 U.S.C. 102(b) as being anticipated by Neri et al, is argued by asserting the antibodies do not exhibit high affinity for the ED-B domain, that a dissociation constant of  $6 \times 10^{-8}$  is not high affinity and is not in the subnanomolar range as recited in claims 28-32.
- 10. It is the position of the examiner that Neri et al claims antibodies of  $6 \times 10^{-8}$  or **LESS** (see claim 14, page 44). The antibody binding specificities are claimed with an upper limit and

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no lower limit, thus clearly defining antibodies with high affinity for ED-B. The smaller the dissociation constant, the higher the binding. With respect to newly submitted claims 33-35, Neri disclosed scFv antibodies, recombinantly produced with a limited number of mutations shown in figure 1B. The rejection is maintained for reasons of record in paper number 15, paragraph 12.

11. The rejection of claims 20-24, and new claims 28-37 and 39 under 35 U.S.C. 103(a) as being unpatentable over Neri et al (WO97/45544) in view of Theodore et al (US Pat. 6,015,897) is asserted as not obviating the claimed invention based upon the recitation of the phrase "high affinity for ED-B domain" in all of the claims. Applicant provided a reference to Viti et al (1999) to show "the desirability of high affinity for the angiogenic properties of the antibody."
12. It is the position of the examiner that Neri et al does disclose antibodies with high binding affinity for ED-B. Neri et al recites a range of binding specificities of  $6 \times 10^{-8}$  or **LESS** (see claim 14, page 44). The Neri reference clearly discloses antibodies with high binding specificity and suggests the selection of antibodies with subnanomolar binding specificities through the recitation of the phrase  $6 \times 10^{-8}$  or **LESS** in claim 14. The person of ordinary skill in the art would have been motivated to select antibodies with binding specificities in the subnanomolar range because Neri et al teaches that antibodies with high binding specificities to the ED-B domain provide the medical professional with a reagent that will

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identify cancerous tissue and can be used as an antibody conjugate in method of delivering cytotoxic agents.

With respect Viti et al, reference provided by Applicant attached to the Amendment submitted March 28, 2001, the antibody, designated "L19" of the reference, it is the position of the examiner that this antibody is not claimed, except in claim 38. Claim 38 has been designated as containing allowable subject matter. Claims 20-24, 28-37 and 39 do not recite the novel and unobvious amino acid sequence, nor the specific binding affinity for the ED-B domain of fibronectin of antibody L19. Neri in view of Theodore is maintained for reasons of record in paper number 15, paragraph 16.

***New Claims/New Claim Limitations/New Grounds of Rejection***

***Specification***

13. The disclosure is objected to because of the following informalities: At page 14, lines 13-20, the nucleic acid sequence and amino acid sequence recited at this location are confusing due to the sequences appearing to be 4 sequences and only two Seq ID Nos shown. Clarification of the sequences is requested.

Table 1, page 27, recites amino acid sequence which should be designated with SEQ ID Nos. to place the application in sequence compliance. Any amino acid sequence of four amino acids or more must be given a SEQ ID NO or reference a larger sequence.

Appropriate correction is required.

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*Claim Rejections - 35 U.S.C. § 112*

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 20, 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. The term "'high affinity for the ED-B domain" in claim 20 is a relative term which renders the claim indefinite. The term "'high affinity for the ED-B domain" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 35 recites the phrase "limited number of mutations". As no upper limit is recited, what is intended is not distinctly claimed. What type of mutations have been introduced? Claim 35 also recites the phrase "mutations in its CDR residues". As these letters are representative of amino acids, clarification of this phrase is requested.

Claim 36 recites specific residues in two domains of the antibodies that have been mutated, but the number of amino acids contained in the antibodies of claim 35 has not been defined. The number of amino acids in the recombinant antibodies can differ, and therefore would



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evidence different numbering schemes. If all of the antibodies comprise the same number of amino acids, amendment of the claim with the SEQ ID NO for the amino acid sequence for the antibody or to define the specific number of amino acids in the antibody would clarify the reference points recited in claim 36, a parent reference sequence has not been defined in the claims.

Claim 36 recites "VH" and "VL", as these letters are designators for amino acids.

Clarification of the meaning of these abbreviations is requested.

### ***Conclusion***

17. This is a non-final action.

18.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp

September 3, 2002

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